REMARKS

Claims 73, 75, 80, 81, 100 to 112, and 115 to 121 are under consideration. By this paper, claims 75, 100 to 105, and 117 to 120 have been cancelled herein without prejudice. Applicants maintain the right to prosecute the cancelled claims in any related application claiming the benefit of priority of the subject application. New claims 122 to 124 have been added. Accordingly, upon entry of this paper, claims 73, 80, 81, 106 to 112, 115, 116 and 121 to 124 are under consideration.

Regarding the Interview on July 1, 2010

Applicants thank the Examiner for the brief interview on July 1, 2010. Due to the time of the interview being insufficient to discuss all issues, Applicants respectfully request an Examiner interview with sufficient time to discuss all remaining issues.

Concerning the interview summary mailed July 7, 2010, Applicants respectfully wish to address several issues therein. First, with respect to the alleged "ambiguous language" in claim 73, namely the language "specifically binds to an epitope...." this language is not ambiguous, as evidenced by the absence of any rejection under 35 U.S.C. §112, second paragraph. Furthermore, this and grammatically similar language have long been accepted by the Patent Office as evidenced by the numerous issued patents with claims with such language. Applicants note that the Examiner had apparently misunderstood the previous remarks, and believe that the remarks on page 16 below will adequately clarify the issue.

Second, with respect to the notion that Applicants are arguing that any antibody can be screened with cross-competing antibodies for epitope binding and is therefore "universally enabled," Applicants were trying to explain to the Examiner that one of skill in the art is starting with heavy and light chain variable sequences of antibody SAM-6, that binds to a target antigen expressed by one of five well defined neoplastic cell lines. As explained in detail below, one of skill in the art could introduce a limited number of mutations, in heavy or light chain variable sequences of SAM-6, in targeted regions using the knowledge in the art concerning antibody structure and function, and then screen the variants for binding using competition assays with SAM-6. This methodology does not suggest that Applicants would obtain any random antibody to evaluate for competition binding. Rather, the skilled artisan already has a functional antibody, SAM-6, and the sequences that confer binding to target. The skilled artisan therefore has the "blueprint" for making additional antibodies based upon SAM-6 sequences. Again, one of skill in the art would merely introduce selected changes to

heavy or light chain variable sequences of SAM-6, and then assay for binding to the antigen to which SAM-6 binds, again, by way of competition binding, for example. Such a methodology of introducing changes into one or more heavy or light chain sequences of a known antibody that binds to a given target antigen and assaying for binding to the same target antigen by way of competition binding was clearly well within the skill in the art at the time of the invention and would not require undue experimentation.

Third, with respect to the statement that "Applicants situation is distinguishable because the antigen much less the epitope is not known," Applicants respectfully point out that the full identity of the antigen to which the claimed antibodies and to which SAM-6 bind, such as the amino acid sequence, simply does not need to be known in order to make additional antibodies, based upon variants of SAM-6, and identify those variants that bind to the antigen to which SAM-6 binds. Again, competition binding with SAM-6 to identify other antibodies (e.g., variants of SAM-6 sequences) can be performed without knowing the full identity of the antigen, such as the amino acid sequence. Thus, whether or not the identify of the antigen to which SAM-6 binds is fully known is simply irrelevant to enablement under 35 U.S.C. §112, first paragraph, of the claims.

Fourth, as discussed in the record, the antigen to which the claimed antibodies and functional fragments bind is defined in terms of expression by at least one of five well defined neoplastic cells lines. The antibodies and functional fragments are also defined in terms of binding to the antigen to which SAM-6 binds. The antigen is therefore adequately defined by such expression and specific binding to SAM-6 such that additional antibodies, based upon variants of SAM-6 sequences, could be identified without undue experimentation.

Regarding the Amendments to the Specification

The specification has been amended to correct an obvious error at page 27, lines 17-21, to correct grams to milligrams. The error is obvious in view of the fact that one of skill in the art knows that the average weight of a mouse is about 20 grams, and therefore that it is impossible for a tumor to weigh 5-8 times more (i.e., about 100-160 grams) than the weight of the mouse itself. Furthermore, the y-axis of Figure 10A, to which the description at page 27 refers, is labeled in increments of 0.05, further indicating that grams in the description is an obvious error. Accordingly, as the amendment was made to correct an obvious error, no new matter has been added and entry thereof is respectfully requested.

The specification has also been amended to recite the correct heavy chain variable region sequence of the SAM-6 antibody produced by the SAM-6 producing hybridoma cell line, and to insert the deposit information for the SAM-6 producing hybridoma, namely, DSM ACC2903. The amendment is supported, for example, at page 61, lines 23-26, which discloses the hybridoma producing SAM-6 monoclonal antibody having the heavy chain variable region sequence. As evidenced by the specific reference to the hybridoma producing SAM-6 antibody, and the accompanying Statement under 37 C.F.R. 1.804(b) executed by Dr. Frank Hensel, Applicants had possession of the hybridoma producing SAM-6 and SAM-6 antibody heavy and light chain variable region sequences at the time the application was filed. Thus, the amendment is supported by the specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Claim Amendments

The amendments to the claims are supported throughout the originally filed specification or were made to address an informality. In particular, the amendment to claim 73 to recite that "said light chain variable region sequence has CDR sequences identical to CDR1, CDR2 and CDR3 of SEQ ID NO:1" or that "said heavy chain variable region sequence has CDR sequences identical to CDR1, CDR2 and CDR3 of SEQ ID NO:3" is supported, for example, by originally filed claim 20, and at page 5, lines 8-21. The amendment to claim 108 to recite "V_H" is supported, for example, by originally filed claim 8. The amendment to claim 111 to recite the correct sequence of heavy chain variable region is supported, for example, at page 61, lines, 23-26, which discloses SAM-6 antibody producing hybridoma, and the accompanying executed Statement under 37 C.F.R. §1.804(b). The amendment to claim 111 was made to provide antecedent basis for the language recited in the amendment to claim 73. Thus, as the claim amendments are supported throughout the originally filed specification or were made to address an informality, no new matter has been added and entry thereof is respectfully requested.

Regarding the New Claims

New claims 122 to 124 are supported throughout the originally filed specification. In particular, claims 122 to 124 are supported, for example, by originally filed claims 1 to 3, and 8, and at page 19, lines 9-15. Thus, as claims 122 to 124 are supported by the originally filed specification, no new matter has been added and entry thereof is respectfully requested.

Regarding the Substitute Sequence Listing

A Substitute Sequence Listing is submitted herewith to correct errors in the sequences. In particular, the listing provides the correct SEQ ID NOs:3 and 4. In particular, the correct SEQ ID NO:4 amino acid sequence has, at position 39, Gln, position 106, Arg, and position 107, Pro. The substitute sequence listing does not add new matter as the correction at position 39 is of an obvious error (translation error, the codon CAG encodes Gln, and not Glu). Support for the corrections at amino acid positions 106 and 107, and the corresponding codons for those positions, is as set forth above for the amendments to the specification. Thus, the Substitute Sequence Listing does not add new matter and entry thereof is respectfully requested.

Regarding Exhibit B

Attached for the Examiner's consideration are binding studies demonstrating that SAM-6 heavy chain variable region sequence alone (VH alone, SEQ ID NO:3), without a light chain variable region sequence, is sufficient to bind to target. In particular, FACS analysis revealed that heavy chain variable region sequence (SEQ ID NO:3) alone binds to HeLa cells. Accordingly, Applicants respectfully request consideration of the accompanying binding data.

Regarding the Objections to the Specification

The specification remains objected to due to the alleged absence of x-axis and y-axis labels for Figure 10A and 10B.

Applicants respectfully point out that the previous remarks in the Response filed November 5, 2009, based upon the specification at page 27, accurately characterize Figures 10A and 10B. In particular, the Examiner's attention is directed to Exhibit A, Figures 10A and 10B attached herewith, in order to assist in the Examiner's understanding. As is evident from Exhibit A, the y-axis of Figures 10A and 10B refer to tumor weight (in grams) and tumor volume (mm^3), respectively, and the circles along the x-axis each represent a particular animal (mouse).

Consistent with Exhibit A, the specification at page 27, lines 16-25, describes the tumor weight (10A) and tumor volume (10B) with numerical values consistent with the numerical values shown on the y-axis. Originally filed Figure 10A y-axis has increments of

0.05, which are increments in grams. As reflected by the amendment to the specification to correct an obvious error in the description at page 27, the weight of the tumors is actually in milligrams and not grams, which corresponds to the y-axis of Figure 10A.

In terms of the circles along the x-axis, consistent with Exhibit A and Applicants' prior clarifying remarks, each circle represents a particular animal (mouse). Thus, Applicants previous remarks in the Response filed November 5, 2009, accurately characterize originally filed Figures 10A and 10B.

Again, Applicants appreciate that control and SAM-6 treated animals are both represented as open circles on originally filed Figure 10. However, in view of the fact that the study results depicted in Figure 10A are described in the specification at page 27, one of skill in the art could clearly "discern the effects of SAM-6 from the control." In particular, the description at page 27, as amended above to reflect the correct units of weight in milligrams, states that "According to Figure 10a the average weight of tumors of SAM-6 treated mice is 96.2 milligrams, while average weight of tumors of mice treated with the control antibody is 150.5 milligrams. Figure 10b shows that analysis of the volume of tumors corresponds to with the analysis of tumor weight. The average volume of tumors of SAM-6 treated mice is 126.3 mm^3, while average volume of tumors of mice treated with control antibody is 158.2 mm^3." Thus, even if Figure 10 by itself does not distinguish SAM-6 from control, clearly in view of the originally filed specification one of skill in the art would understand the effect of SAM-6 as compared to control.

Applicants again note that submission of a revised Figure 10 or additional description of the results may prompt a rejection for addition of new matter, and respectfully request the Examiner's consideration in this respect. Furthermore, in view of the fact that one of skill in the art would clearly understand the effect of SAM-6 compared to control based upon the description at page 27 of the originally filed specification, Applicants submit that there is no need to amend Figure 10 or the description of the results, and respectfully request withdrawal of the objection.

REJECTIONS UNDER 35 U.S.C. §112, FIRST PARAGRAPH

ENABLEMENT

The rejection of claims 100 to 111 and 117 to 120 under 35 U.S.C. §112, first paragraph as allegedly lacking enablement is respectfully traversed. According to the Patent

Office, allegedly it would require undue experimentation to make and use the claimed invention.

Claims 100 to 105, and 117 to 120 have been cancelled herein without prejudice. Thus, the rejection of these claims is moot. The rejection will therefore be addressed with respect to claims 106 to111.

Applicants respectfully point out that claim 73 have not been rejected as allegedly lacking enablement. However, claims 106 to 111, which depend from claim 73, have been rejected as allegedly lacking enablement. Applicants respectfully request clarification on how independent claim 73 is adequately enabled, but claims that depend from claim 73 and are therefore more limited in scope than claim 73, allegedly lacking enablement.

As previously pointed out in the record, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention relevant to antibodies, antibody variants having the requisite activity could be produced and identified using routine methods disclosed in the specification or that were known in the art at the time of the invention without undue experimentation. Importantly, such methods do not require more detailed knowledge of antigen identity since the antigen is expressed by at least one of five well-defined neoplastic cell lines and SAM-6 antibody binds to the antigen. Consequently, one skilled in the art could make and use the claimed antibodies and functional fragments without undue experimentation.

Applicants first wish to address what appears to be a primary ground for maintaining the rejection, namely the inability to "predict the kind and extent of modification for the variable domains in order for the resultant claimed antibody to meet the functional requirements of the claims," or that the skilled artisan "could not predict the hotspots much less those residues critical for conferring specific antigen binding." As discussed in the record, there is no need for one of skill in the art to have to predict or know the hotspots or critical residues in order to make and use the claimed antibodies without undue experimentation. Here, methods of making variant antibodies and functional fragments and identifying those with activity (e.g., binding, inhibit cell proliferation, etc.) are disclosed in the specification and/or were routine at the time of the invention, and the level of knowledge and skill in the art regarding making antibodies and functional fragments thereof at the time of the invention was high.

For example, methods of producing antibodies and amino acid variants without undue experimentation are disclosed in the specification (page 31, line 20, to page 36, line 26) and

were also known in the art at the time of the invention. Methods of producing antibody fragments (*e.g.*, Fv, Fab, Fab' and $F(ab')_2$) were known in the art and were routine at the time of the invention. Methods of identifying antibodies and fragments that bind antigen without undue experimentation are taught by the specification and were also known in the art. In particular, routine methods for detecting antibody binding to antigen or cell lines (e.g., by Western analysis, ELISA or co-immunoprecipitation, page 18, line 23 to page 19, line 7), as well as methods for measuring cell proliferation and apoptosis are disclosed in the specification (page 47, line 8 to page 49, line 10; page 55, line 26, to page 57, line 29; and page 66, line 10, to page 68, line 24). Thus, in view of the guidance in the specification and the high level of knowledge and skill in the art at the time of the invention, one skilled in the art could readily make antibodies and functional fragments without undue experimentation. Consequently, there is no need for one of skill in the art to have to predict or to know the hotspots or critical residues in order to produce antibodies and functional fragments within the scope of the claims. For example, the skilled artisan could simply introduce mutations in a heavy and/or light chain variable region (SEQ ID NOs:1 or 3) and then verify which antibodies and fragments bind to at least one of the neoplastic cells that express the antigen to which SAM-6 antibody binds (e.g., via competition binding).

In sum, one of skill in the art need not predict or know in advance the effect of any particular sequence variation on binding in order to produce functional variant antibodies and functional fragments. Nor would one of skill in the art need additional knowledge of antigen identity in order to produce such functional variant antibodies and functional fragments.

To corroborate that variant antibodies having binding activity could be produced at the time of the invention without predicting in advance substitutions that would function and without undue experimentation, previously submitted Exhibit A (Boder *et al.*, Proc. Nat'l Acad. Sci. USA 97:10701 (2000)) describe directed evolution of scFv fragments, and generation of a large number of Fv sequences with improved binding affinity compared to non-mutagenized antibody. Notably, the authors made no effort and did not need to predict or know in advance which substitutions would function. The authors stated "[t]he relative ease with which extremely high affinity has been attained in this study." (page 10705, first column, last full paragraph) Consequently, in view of the fact that variants with improved affinity could be made "with relative ease" at the time of the invention without predicting or knowing in advance substitutions that would function, one of skill in the art could clearly produce variant antibodies and fragments having at least some detectable binding affinity,

inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

Applicants also respectfully point out that the previously submitted Declaration under 37 C.F.R. §1.132, executed by Dr. Peter Vollmers evidences that one of skill in the art could produce variant antibodies and fragments having at least some detectable binding affinity, inhibit cell proliferation or induce apoptosis without undue experimentation at the time of the invention. The facts and Dr. Vollmers' conclusions based upon the facts are summarized in the Declaration, Paragraphs 20-24. Accordingly, the Declaration under 37C.F.R. §1.132, executed by Dr. Peter Vollmers additionally corroborates that one of skill in the art could produce variant antibodies and functional fragments having binding affinity, inhibit cell proliferation or induce apoptosis, without undue experimentation at the time of the invention.

Furthermore, the amended claims expressly recite sequence identity to the predicted CDRs of SAM-6 in the regions known to confer antigen binding specificity and affinity. Thus, in view of the fact that the claimed antibodies and functional fragments include the predicted CDRs of heavy or light chain sequences specified by SEQ ID NOs:1 or 3, the claimed antibodies and functional fragments share significant sequence identity with SAM-6 in the regions known to confer antigen binding specificity and affinity.

Lastly, Applicants respectfully reiterate that there is no authority requiring enablement under 35 U.S.C. §112, first paragraph to be satisfied by a particular methodology identified by the Patent Office to the exclusion of other methodologies. Here, the Patent Office continues to insist that the claims lack enablement due to the purported inability of one of skill in the art to predict or know the hotspots or critical residues of the antibodies and functional fragments. However, the Patent Office cannot insist that Applicants demonstrate enablement by a particular method, namely predicting or knowing the hotspots or critical residues of the antibodies and functional fragments within the scope of the claims. As clearly demonstrated by previously submitted Exhibit A (Boder *et al.*), there is no need for one of skill in the art to predict or know in advance substitutions that would function in order to produce variant antibodies and fragments having at least some detectable binding affinity, inhibit cell proliferation or induce apoptosis. Consequently, in applying the correct standard for enablement under 35 U.S.C. §112 Applicants respectfully request consideration of the foregoing methods, the comments in the record and the corroborating Exhibits evidencing that prediction or knowledge of hotspots is not required to make antibodies and fragments without undue experimentation.

Turning to the grounds for rejection due to differences with the facts in *In re Wands*, Applicants appreciate that the technology has advanced substantially between 1981 and the time that the subject application was filed in 2003. However, for the reasons discussed above and in the record, there is no need to "calculate" variable domain modifications or amino acid frequency alignment in order to make antibody variants without undue experimentation. Furthermore, additional knowledge concerning antigen identity is not required since the assays to ascertain binding, apoptosis and cell proliferation do not require additional knowledge of the antigen. The point Applicants were making is that even as far back as 1981 one of skill in the art could readily identify antibodies that bind to a given target without undue experimentation. The factual analogy with *Wands* applies to the subject claims because again all that is required in order to make and identify antibodies and functional fragments within the scope of the claims is to produce a variant, and ascertain binding to antigen expressed by at least one of the neoplastic cell lines recited in claims 73 or 122 to which SAM-6 binds, which as discussed above and in the record can be determined by competition binding in the presence of SAM-6 antibody. Such competition binding assays, known in the art at the time of the invention, do not require additional knowledge of antigen since the binding identifies antibodies that bind to the antigen to which SAM-6 binds without such knowledge. Consequently, the factual analogy to *Wands* is appropriate, and given the guidance in the specification, and particularly the high level and substantial advances in the knowledge and skill in the antibody art in 2003 as compared to 1981, clearly making and identifying variant antibodies and fragments within the scope of the claims would not require undue experimentation.

In sum, in view of the guidance in the specification and knowledge in the art at the time of the invention, the publications of record, and the previously submitted Declaration under 37C.F.R. §1.132 executed by Dr. Peter Vollmers, the skilled artisan could readily produce and identify antibody variants and functional fragments of SEQ ID NO:1 and 3 without undue experimentation. Consequently, the claims are adequately enabled under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

WRITTEN DESCRIPTION

The rejection of claims 73, 75, 80, 81, 100 to 112 and 115 to 121 under 35 U.S.C. §112, first paragraph as allegedly lacking an adequate written description is respectfully traversed. According to the Patent Office, allegedly the claims contain subject matter which

is not adequately described in the specification to reasonably convey to one skilled in the art that Applicants had possession of the invention.

The claims are adequately described under 35 U.S.C. §112, first paragraph. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claims 75, 100 to 105, and 117 to 120 have been cancelled herein without prejudice. Thus, the rejection of these claims is moot. The rejection will therefore be addressed with respect to amended claims 73, 80, 81, and 106 to 111.

Applicants first point out that with respect to claims 80 and 81, these claims recite the light and heavy chain variable regions of SAM-6, namely SEQ ID NOs:1 and 3, respectively. Consequently, as the antibodies and functional fragments are defined by SEQ ID NOs:1 and 3, claims 80 and 81 are therefore adequately described under 35 U.S.C. §112, first paragraph.

Turning to the grounds for rejection in the Action at pages 18 and 19, Applicants agree that specific binding does not mean exclusive binding. What Applicants had intended to convey in the prior response distinguishing the claims from the *Alonso* decision is that the claimed antibodies and functional fragments have the same specificity and bind to a single epitope, namely the epitope of the antigen expressed by at least one of the specified neoplastic cells to which the SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 specifically binds. Applicants comments were not intended to exclude the possibility that the claimed antibodies bind to another antigen that shares the same epitope to which SAM-6 antibody binds. Accordingly, Applicants apologize for any confusion that may have been caused by the prior remarks.

As the Examiner correctly points out, an epitope may be present on more than one antigen, and therefore an antibody that specifically binds to one antigen may also specifically bind to another antigen that shares the same epitope. As also correctly pointed out by the Examiner, specific binding is not the same as exclusive binding. Applicants did not intend to infer exclusive binding in the claims. In view of the foregoing clarification, Applicants believe that this ground for rejection is moot.

In terms of any other grounds for rejection remaining for lack of written description, as previously stated the law does not require an actual reduction to practice or disclosure of a specific number of examples within the scope of the claims to satisfy the written description requirement under 35 U.S.C. §112, first paragraph. *In re Angstadt*, 537 F.2d 498, 502-503 (CCPA 1976), *Utter v. Hiraga*, 845 F.2d 993, 998-99 (Fed. Cir. 1988). In particular, "(1) examples are not necessary to support adequacy of a written description (2) the written

description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 448 F.3d 1357 (Fed. Cir. 2006). Consequently, actual reduction to practice is not required to satisfy written description under 35 U.S.C. §112, first paragraph.

Again, the claimed antibodies and functional fragments bind to an epitope of an antigen that SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 binds, and the antigen is expressed by at least one of the five specifically recited neoplastic cell lines. Thus, the epitope of the antigen is defined in terms of 1) expression by at least one of the neoplastic cell lines; and 2) binding to SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3. Thus, one of skill in the art would know, without having to know anything more about the identity of the epitope or the antigen, antibodies and functional fragments within the scope of the claims. For example, one skilled in the art would know that competition binding is a simple and routine technique known in the art at the time of the invention to verify that a given antibody or functional fragment binds to an antigen to which a reference antibody (e.g., SAM-6) binds. Thus, an antibody or functional fragment that competes for SAM-6 binding to antigen expressed by at least one of the specified neoplastic cell lines would be within the scope of the claims, whereas an antibody that did not compete for SAM-6 binding to at least one of the specific cell lines would not be within the scope of the claims. Consequently, one of skill in the art needs no additional information about epitope or antigen identity in order to know antibodies and functional fragments within the scope of the claims.

Second, the claimed antibodies and functional fragments are described structurally and functionally. In this regard, antibodies that bind to a common epitope typically share sequence homology, such as in CDR3 of heavy chain variable region. Thus, antibodies that bind to the same epitope as SAM-6 will inherently share sequence identity to SEQ ID NO:1 and/or SEQ ID NO:3. Furthermore, the amended claims require identity to 3 of the predicted CDRs of SEQ ID NOs:1 or 3. Thus, the claimed antibodies and functional fragments share a common functional (epitope binding) and structural (sequence identity) relationship with SAM-6. Consequently, the claimed antibodies and functional fragments are described both structurally and functionally.

Third, the knowledge and skill in the art in terms of antibody structure correlating with function at the time of the invention was high, as previously discussed. The role of antibody heavy and light chain variable regions, particularly CDRs and FRs, in antigen

binding is disclosed in the specification and was well understood by the skilled artisan at the time of the invention. Consequently, the level of knowledge and skill in the art with respect to antibody structure (CDRs, FRs, D- and J-regions, etc.) correlating with function was high at the time of the invention.

Fourth, the specification discloses antibody variable light and heavy chain region sequences (e.g., SEQ ID NOs:1 and 3), the predicted sequences and positions of CDRs (page 5, lines 11-21; and Sequence Listing), and therefore also the location of the FRs. Consequently, the skilled artisan would know the predicted locations and amino acid sequences of all CDRs and FRs of SEQ ID NOs:1 and 3 that contribute to antigen binding.

Fifth, because the knowledge and skill in the art in terms of antibody structure correlating with function was high and the location and sequences of predicted CDRs and FRs in SEQ ID NOs:1 and 3 that contribute to antigen binding would be known, the skilled artisan would also have known residues in SEQ ID NOs:1 and 3 amenable to substitution. For example, the skilled artisan would know that an amino acid substitution, such as a conservative substitution, insertion or a deletion, for example, outside of a CDR or FR region of in SEQ ID NOs:1 and 3 would likely not destroy antigen binding activity. Thus, because the level of knowledge and skill in the art with respect to antibody structure correlating with function was high at the time of the invention, and the sequence regions important for conferring antigen binding were known, one skilled in the art could have predicted with a high degree of confidence many substitutions of SEQ ID NOs:1 and 3 that would not destroy binding activity. Moreover, as previously pointed out, changes in antibody CDRs and FRs are more permissive than what the Patent Office acknowledges, as evidenced by previously submitted Exhibits B-E, each reporting that substitutions or deletions/insertions of amino acids within antibody CDRs (i.e., CDR1, CDR2 or CDR3) or FRs were well tolerated.

Again, the facts of the claimed antibodies and functional fragments, in which there was a high degree of knowledge of structure and function at the time of the invention, are analogous to the facts in *Invitrogen Corp. v. Clontech Laboratories, Inc.*, 429 F.3d 1052 (Fed. Cir. 2005), in which the court held that a single embodiment of a protein (a reverse transcriptase (RT)) provided an adequate written description for claims directed to a genus of such proteins. The court significantly relied upon the fact that the single disclosed embodiment had 1) sufficient correlation between structure and function; and 2) shared significant homology with others. In affirming that the patent claims satisfied the written description requirement, as articulated in *Regents of the University of California v. Eli Lilly &*

Co., 119 F.3d 1559 (1997) and *Fiers v. Revel*, 984 F.2d 1164 (Fed. Cir. 1993), the court held that "the shared written description for the patents-in-issue recites both the DNA and amino acid sequences of a representative embodiment of the claimed RT enzyme. The specification also discloses test data that the enzyme produced by the listed sequence has the claimed features—DNA polymerase activity without RNase H activity. Under both the *Eli Lilly* and *Fiers* analysis, the specification at bar is sufficient. In short, there is no error in the district court's ruling that the claims in the patents-in-suit satisfy the written description requirement of §112." Thus, the claims of the patents-in-issue in *Invitrogen*, which did not recite a particular amount of homology or identity to a reference sequence in the claims, satisfied the written description requirement even though there was only a single disclosed embodiment in the specification. In view of *Invitrogen*, a single embodiment provides an adequate written description of a genus of proteins where there is sufficient correlation between protein structure and function, and the members of the species share significant homology.

Once again, as in *Invtrogen* there was substantial understanding of antibody structure correlating with function at the time of the invention, and the antibody light and heavy chain variable region sequences including predicted positions and sequences of all CDRs and therefore the location and sequences of all FRs, and as such all sequences that mediate antigen binding are disclosed in the specification. The claimed antibodies and functional fragments also share common structural (sequence homology) and functional (bind to the epitope to which SAM-6 antibody binds) attributes. Consequently, the facts of the claims under consideration are analogous to the facts in *Invitrogen.*

Applicants also respectfully reiterate that *In re Alonso* is inapposite to the claims of the application. First, the *Alonso* claims are directed to methods of treating neurofibrosarcomas, using antibodies idiotypic to the neurofibrosarcomas, and the antibodies in *Alonso* were not limited to binding to any particular epitope or antigen. Instead, the genus of antibodies encompassed by the *Alonso* claims could bind to any epitope and any antigen expressed, which epitopes and antigens had different and unknown specificities. Thus, the claimed treatment methods of *Alonso* encompassed antibodies not limited to binding to any particular epitope or antigen.

In contrast to the antibodies of *Alonso*, the claimed antibodies and functional fragments have the same specificity and bind to a single epitope, namely the epitope of the antigen expressed by at least one of the specified neoplastic cells to which the SAM-6 antibody comprising SEQ ID NO:1 and SEQ ID NO:3 specifically binds. Also in contrast to

Alonso, the claimed antibodies and functional fragments bind to antigen expressed by at least one of five well defined deposited neoplastic cell lines.

Second, the antibodies in *Alonso* were not defined by or limited to any structure. In contrast to the *Alonso* antibodies, the amended claims are directed to antibodies and functional fragments having sequence identity to SEQ ID NOs:1 and 3 due to 1) binding to the same epitope as SAM-6; and 2) as expressly recited to be identical to predicted CDRs of SEQ ID NOs:1 or 3 of SAM-6. Thus, the claimed antibodies and functional fragments share a common structure (amino acid residues) by virtue of binding to the same epitope, and as expressly recited in the amended claims.

Third, the patent application at issue in *Alonso* (USSN 08/469,749) claimed priority to an application filed in 1988. In contrast, the subject application claims priority to an application filed November 11, 2003, which is at least 15 years after the *Alonso* priority application was filed. Obviously, the state of knowledge in the art concerning antibody structure correlating with function was greater 15 years later in 2003 than in 1988. Indeed, the state of the art was so much more advanced in 2003 that a finding based upon the state of the art in 1988 is wholly insufficient to make a factual evaluation of an invention in 2003.

As an example of the advanced state of the art, previously submitted Exhibit 2 indicated that substitutions of framework residues of humanized antibodies with donor framework residues improved antibody affinity (Foote and Winter, J. Mol. Biol. 224:487 (1992)). Previously submitted Exhibits 1 and 3, in 1998 and 2000, respectively, reported that CDR3 of heavy chain variable region was the principal determinant of antigen recognition and specificity, indicating that one of skill in the art would know that heavy chain CDR1 and CDR2 are less important for antigen specificity compared to heavy chain CDR3. As yet another example of the advanced state of the art, previously submitted Exhibit 4 reported the role of FRs and CDRs in antibody function, that FRs have conserved substitutions, that CDR3 has a primary role in antigen specificity, and that particular amino acid residues are more prevalent in CDRs/FRs. Still another previously submitted publication (Exhibit 5) reported the construction of a fully human combinatorial antibody library based upon human consensus FRs and CDRs further evidencing the advanced state of the art. Consequently, one of skill in the art would know antibody sequence regions more or less amenable to substitution, the types of amino acid residues that are most prevalent and/or tolerated at given positions and could therefore deduce functional variants based upon this knowledge.

In sum, the knowledge in the art concerning antibody structure correlating with function was significantly greater in 2003 than in 1988. Consequently, one of skill in the art would have been able to reasonably predict with a high degree of confidence variants of SEQ ID NO:1 and 3 that would retain binding.

Further examples of the advanced state of the art were submitted as Exhibit 6, which reported that heavy chain variable region sequences could productively pair with a variety of different light chain variable region sequences and maintain antigen binding specificity (see, e.g., abstract, a heavy chain could productively pair with a light chain and still maintain HIV gp120 antigen binding activity from 43% -100%). Even unrelated light chain variable region sequences (to tetanus toxoid) productively paired with a heavy chain variable region sequence (to HIV gp120) to produce an antibody that maintained binding to HIV gp120 with a high degree of frequency (page 10029-10030). Thus, one of skill in the art would have known that the heavy chain variable region sequence can productively pair with a number of light chain variable region sequences and retain antigen specificity, indicating that variations to the light chain variable region sequence are tolerated.

Indeed, reports indicate that light chain may not be required for binding at all to a target antigen. Submitted herewith as Exhibit B is data indicating that heavy chain variable region sequence (SEQ ID NO:1) confers much if not all of the binding to antigen. In brief, SAM-6 variable region heavy chain, without light chain, was analyzed for binding to HeLa cells, as compared to SAM-6 with both VH and VL chains (positive controls) and scFv and IgM (negative controls). The data revealed that SAM-6 variable region heavy chain alone bound to HeLa cells (Exhibit B, Figure A). This data is consistent with the contribution of heavy chain variable region sequence to antigen binding and specificity, and confirms that light chain variable region sequence is not required for antigen binding.

Furthermore, in view of the fact that the claimed antibodies and functional fragments have identical specificity, bind to a single epitope and share a common structure, unlike the *Alonso* antibodies, and that the state of the art at the time of that the application was filed was more advanced as compared to the state of the art of the application at issue in *Alonso*, the claims under consideration are highly distinguishable from the claims at issue in the *Alonso* decision.

Lastly, again, the *Alonso* court did not consider the merits of the argument that the antibodies were adequately described in view of the well-known correlation between structure and function of antibodies since they were not raised during proceedings before the

Board. Consequently, given the fact that arguments pointing out the well-known correlation between structure and function of antibodies were not considered by the *Alonso* court, the *Alonso* decision does not stand for the proposition that antibodies are not adequately described in spite of well-known correlation between structure and function of antibodies, particularly given the advances in the state of the art in the 15 years after the *Alonso* priority application was filed.

In sum, the facts of the claimed antibodies and functional fragments are readily distinguishable from *Alonso*, in that the claimed antibodies and functional fragments 1) have the same specificity and bind to a shared epitope expressed by at least one of five well-defined neoplastic cell lines; 2) share a common sequence structure due to binding to a common epitope and as specifically required by amended claim 73; and 3) unlike *Alonso*, the far more advanced knowledge in the art concerning antibody structure correlating with function. Furthermore, in reaching its decision the *Alonso* court failed to consider the well-known correlation between structure and function of antibodies.

Additionally, the previously filed Declaration under 37 C.F.R. §1.132 executed by Dr. Peter Vollmers verifies that the claims are adequately described under 35 U.S.C. §112, first paragraph. Dr. Vollmers provided objective facts, and conclusions based upon the objective facts, in the previously filed Declaration, at paragraphs 6 to 19.

In sum, given the totality of: Guidance in the specification and the high level of knowledge and skill in the art with respect to antibody structure correlating with function at the time of the invention, knowledge of the light and heavy chain variable region sequences (SEQ ID NOs:1 and 3) and the predicted CDRs and FRs that confer binding, as also corroborated by the Exhibit submitted herewith and the previously submitted Exhibits and Declaration under 37 C.F.R. §1.132 executed by Dr. Vollmers, the skilled artisan would know of general regions and particular residues that would be amenable to variation and would therefore be apprised of a number of sequence variants of SEQ ID NOs:1 and 3 having binding activity, the claims meet the written description standard articulated by the court in *Invitrogen*. Further in view of the substantially greater understanding of antibody sequence structure and correlation with function in 2003 compared to 1988, and that the claimed antibodies and fragments will have the specificity of SAM-6 antibody comprising SEQ ID NOs:1 and 3, and will also necessarily have sequence homology with SEQ ID NOs:1 or 3, the facts of the claims under consideration are clearly distinguishable from the facts in *Alonso*.

Consequently, the claims are adequately described under 35 U.S.C. §112, first paragraph, and the rejection must be withdrawn.

REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

The rejection of claim 75 under 35 U.S.C. §112, second paragraph as allegedly indefinite is respectfully traversed. According to the Patent Office, the cancer cells of dependent claim 75 are broader than independent claim 73.

Claim 75 is clear and definite. Nevertheless, solely in order to further prosecution of the application and without acquiescing to the propriety of the rejection, claim 75 has been cancelled herein without prejudice. Thus, the rejection under 35 U.S.C. §112, second paragraph is moot.

CONCLUSION

Please charge any fees associated with the submission of this paper to Deposit Account Number 033975. The Commissioner for Patents is also authorized to credit any over payments to the above-referenced Deposit Account.

Respectfully submitted,

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